REMARKS

The claimed invention relates to the identification and use of diagnostic markers for distinguishing amongst a plurality of cardiovascular disorders. The present claims refer to methods that comprise assaying a sample for the presence or amount of one or more subject-derived markers related to blood pressure regulation, and for the presence or amount of one or more subject-derived markers related to myocardial injury, and characterizing the subject's risk of having developed or of developing each cardiovascular disorder based upon the presence or amount of the markers measured. As described in detail in the specification, in certain embodiments, this characterization is performed without comparing the amount of one or more of the markers measured to a predetermined threshold amount.

Prior to the present submission, claims 1-36 were pending in the application, with claims 1-17 under examination. Claims 18-36, which were withdrawn from consideration by the Examiner according to a restriction requirement, are cancelled herein. Claims 1, 2, 4-6, 8-10, 12-14, and 17 are amended herein for purposes of clarifying the invention for the benefit of the Examiner as described hereinafter. These amendments do not introduce new matter, or alter the scope of the amended claims. Additionally, Applicants have added new claims 37-38, which are directed to subject matter that the Examiner acknowledges is enabled by the present specification.

Applicants expressly reserve the right to claim subject matter not yet or no longer claimed in one or more applications that may claim priority hereto. Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non-Art Based Remarks

1. Information Disclosure Statement

A replacement PTO/SB08 submitted April 14, 2003 revised in accordance with the Examiner's suggestions is attached herewith.

Applicants note that section 5 on page 4 of the Office Action concerns a listing of references cited by the examiner in related application. The Examiner has initialed all the listed references. Applicants note for the record that the additional copies of the 892 forms which gave rise to that submission are not themselves a formal submission but are supplied only as a convenience to the Examiner.

2. Specification

The Examiner has objected to the Sequence Listing submitted by Applicants, believing that SEQ ID NO: 3 introduces new matter. Applicants respectfully submit that the Examiner is in error. The sequence recited in the Sequence Listing as SEQ ID NO: 3 may be found in paragraph [0213] of the specification as filed. Applicants request that the objection be reconsidered and withdrawn.

The Examiner has also requested that certain trademarks used in paragraphs [0239] and [0252] be capitalized and accompanied by generic terminology. Applicants thank the Examiner for the careful reading of the specification, and have amended the paragraphs accordingly.

3. Rejection of claims 1-10, 13, and 15-17 under 35 U.S.C. § 112, first paragraph (written description)

Applicants respectfully traverse the rejection of claims 1-10, 13, and 15-17 as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Pending claim 1 refers to a method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders. These methods comprise assaying the sample for the presence or amount of *one or more subject-derived markers related to blood pressure regulation*, and for the presence or amount of *one or more subject-derived markers related to myocardial injury*. Based upon the presence or amount of the markers measured, the results of the assays performed are used to characterize the subject's risk of having developed or of developing the plurality of cardiovascular disorders.

The term "subject-derived marker" is defined in the present specification, *e.g.*, in paragraph [0068]. Claim 1 refers to a plurality of subject-derived markers from certain specified art-recognized marker classes (markers related to blood pressure regulation and markers related to myocardial injury), as do dependent claims 5 and 9 (which refer to "markers related to inflammation" and "markers related to coagulation and hemostasis," respectively). The skilled artisan understands that these art-recognized marker classes refer to markers having relationships to well known physiological pathways.

For example, a subject-derived marker "related to myocardial injury" as that term is used in the art refers to certain detectable macromolecules that are expressed by the cells of a subject, the levels of which are related to the presence of a myocardial injury. Members of this marker class, which include myoglobin, cardiac troponins, creatine kinase-MB, etc., have long been well known in the art. *See, e.g.*, Kemp *et al.*, *Br. J. Anaesthesia* 93: 63-73 (2004) for a review of the literature. (Copy of reference provided in association with an IDS filed herewith) Likewise, a subject-derived marker "related to blood pressure regulation" is a detectable macromolecule that is expressed by the cells of a subject and that has a relationship with blood pressure regulation. The specification provides numerous examples of this category of markers, including natriuretic peptides such as BNP. Such markers are known in the art to play a "key role in salt and water homeostasis and blood pressure regulation through direct vasodilator, diuretic, and natriuretic properties." Freitag *et al.*, *Hypertension* 41: 978-83 (2003). (Copy of reference provided in association with an IDS filed herewith) Similarly, a subject-derived marker "related to inflammation" is a detectable macromolecule that is expressed by the cells of a subject and that has a relationship with inflammation. This category of marker is well known and well studied in the art. *See, e.g.*, Biasucci, *Circulation* 110: e560-e567, 2004. The present specification again provides numerous examples of such markers. And a subject-derived marker "related to coagulation and hemostasis" is a detectable macromolecule that is expressed by the cells of a subject and that has a relationship with coagulation and arresting of bleeding ("hemostasis"). As is well known in the art, such markers "allow the detection of *in vivo* coagulation activation." Fassbender *et al.*, *Stroke* 30: 2101-4 (1999). (Copy of reference provided in association with an IDS filed herewith) And again, the specification provides numerous examples of this category of markers.

As demonstrated by the articles cited in the preceding paragraph, Applicants note that there is nothing unusual in the art with regard to referring to these biomarkers generally by reference to their art-recognized classes. Reference to art recognized classes of biomarkers also is reflected in issued U.S. Patents. See, e.g., U.S. Patent No. 5,604,105, which refers to a method of diagnosing chest pain using three "markers of cardiac damage"; and U.S. Patent No. 6,040,147, which refers to a method of characterizing risk in cardiovascular diseases by correlating "a level of a marker of systemic inflammation" to an individual's risk.

The Examiner takes the position that written description is lacking since "the claims are not limited as to the number of markers." Office Action, page 8. To the extent that the argument is due to the use of "comprising" in the claims, which opens the claim to additional biomarkers that can be combined to provide a large number of individual panels, Applicants respectfully submit that this is always true of claims written in "comprising" form, which are construed to include additional unrecited elements or method steps, and so are open to literally an infinite number of theoretical modifications and variations. The use of open language in claims that clearly recite the markers that are required to be measured, as in the present case, is standard and accepted practice (again Applicants refer, only by way of example, to U.S. Patent Nos. 5,604,105 and 6,040,147, which are also written in comprising form, and so presumably optionally include any possible combination of markers) and cannot support a *prima facie* case of a lack of written description.

The Examiner also takes the position that written description is lacking since "the prior art does not teach methods of determining all possible panels to distinguish amongst a plurality of cardiovascular disorders." Office Action, page 8. Applicants question the relevance of a discussion of the teachings of the "prior art" in an analysis of whether or not the present application meets the written description standard. As stated in *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956), "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

The Examiner also states that, because each biomarker is a unique polypeptide, "any given markers would not be capable of distinguishing 'all cardiovascular disorders.'" Office Action, page 8. Applicants note that the pending claims do not relate to methods that distinguish

all cardiovascular disorders, and question the relevance of this assertion to a written description analysis of the pending claims. Moreover, the Examiner's argument completely ignores the fact that the present claims refer to art-recognized classes of biomarkers. The skilled artisan understands the relationship of these markers to their respective physiological pathways. The fact that each biomarker is a different polypeptide is not a meaningful distinction in the context of the present claims, as each member of a particular marker class is related, not by sequence, but by its established physiological relationships.

The Examiner acknowledges that the specification provides exemplary data for 9 different marker combinations for distinguishing a plurality of cardiovascular disorders, including "myocardial infarction, congestive heart failure, acute coronary syndromes, unstable angina, and pulmonary embolism." Applicants note that these examples include markers selected from each of the classes of markers recited in the present claims, including markers related to blood pressure regulation (*e.g.*, ANP, BNP, and CGRP), markers related to myocardial injury (*e.g.*, cardiac troponin, myoglobin, and CK-MB), markers related to inflammation (e.g., CRP) and markers related to coagulation and hemostasis (*e.g.*, D-dimer). While the Examiner acknowledges sufficient written description insofar as the present application provides actual examples, Applicants respectfully submit that it is not proper to focus the written description analysis on the examples alone, all the while ignoring the rest of the specification. Nor is it the task of the claims to exclude hypothetically inoperable embodiments:

> Nor are we concerned that the claims may include inoperable embodiments, as is it not a function of the claims to specifically exclude possible inoperative embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974). The Federal Circuit has cautioned against limiting a claimed invention to preferred embodiments or specific examples set forth in the specification. Texas Instruments v. U.S. Int'l Trade Comm., 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986).

Ex Parte Hicks, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.).

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir.

1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* An adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a).

Applicant respectfully submits that the specification is sufficient to reasonably convey to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. 35 U.S.C. § 112, first paragraph demands no more. In view of the foregoing, Applicant urges the Examiner to withdraw the written description rejection of claims 1-10, 13, and 15-17.

4. Rejection of claims 1-10, 13, and 15-17 under 35 U.S.C. § 112, first paragraph (enablement)

Applicant respectfully traverses the rejection of claims 1-10, 13, and 15-17 as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner acknowledges that the specification is enabling for a method for distinguishing between myocardial infarction and pulmonary embolism using subject-derived markers comprising troponin isoforms, B-type natriuretic peptide, and D-dimer. But the Examiner asserts that the specification does not enable methods to distinguish amongst a plurality of cardiovascular disorders, where the markers used are markers related to blood pressure regulation, myocardial injury, inflammation, and coagulation and hemostasis. Office Action, page 9.

In rejecting the claims, the Examiner seeks to focus the enablement analysis on what is present in specific examples, while ignoring the remaining teachings of the specification. The Federal Circuit has cautioned against limiting a claimed invention to preferred embodiments or specific examples in this manner. See, *Ex Parte Hicks*, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.) (citing *Texas Instruments v. U.S. Int'l Trade Comm.*, 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986)). The proper test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. As the following analysis demonstrates, the present claims meet this standard.

The factors relevant to an enablement analysis are enumerated in *In re Wands*, so Applicant has attempted to address the Examiner's remarks in the context of the various *Wands* factors.

A. The nature of the invention

The present invention is related to the use of biomarker measurements to diagnose cardiovascular disorders. In particular, claim 1 provides that at least one subject-derived marker related to blood pressure regulation and at least one subject-derived markers related to myocardial injury are used to distinguish between different cardiovascular disorders, for example congestive heart failure and cardiac ischemia and necrosis. The addition of markers such as those related to inflammation and to coagulation and hemostasis can be used, for example, to further distinguish amongst other cardiovascular disorders such as pulmonary embolism, aortic dissection, and deep vein thrombosis. *See, e.g.*, Specification, paragraphs [0227]-[0264].

B. The state of the prior art

Applicants agree with the Examiner's view of the general state of the prior art as described in the Office Action section bridging pages 14 and 15 that biomarkers are routinely used in the art for diagnosis and prognosis of individual cardiac conditions.

As for the specific classes of subject-derived markers recited in claim 1, a review written by Kemp *et al.*, *Br. J. Anaesthesia* 93: 63-73 (2004) (Copy of reference provided in association with an IDS filed herewith), notes that the first account of the use of biochemical markers related to myocardial injury was published in 1954, and that the identity and use of a large number of such markers are well known. *See, e.g.*, Kemp *et al.* page 65, Table 2. Likewise, markers related to blood pressure regulation, and in particular natriuretic peptides such as ANP and BNP, and their biosynthetically related fragments such as NT-proANP and NT-proBNP, have found use in the diagnosis of congestive heart failure. *See, e.g.*, Felker *et al., CMAJ* 175: 611-617 for review. (Copy of reference provided in association with an IDS filed herewith)

With regard to the specific classes of subject-derived markers recited in the dependent claims, markers "related to inflammation" and "related to coagulation and hemostasis" are also well known. *See, e.g.*, Biasucci, *Circulation* 110: e560-e567, 2004, and Fassbender *et al.*, Stroke 30: 2101-4 (1999).

The Examiner refers to several publications in an attempt to paint the state of the prior art in a negative light. Many of these comments amount to a recitation of difficulties that *might* be encountered in practice in the general use of biomarkers. That type of reasoning is not a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3. In addition, the Examiner's assertions about the limits of the prior art are not well founded.

For example, the Examiner states that Bast *et al.*, *Clin. Cancer Res.* 11: 6103-8, 2005, "point to the 'lengthy process' of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically." Office Action, page 14. In addition to being merely a recitation of difficulties that *might* be encountered in practice, the Examiner has failed to acknowledge that this "lengthy process" quote, which is found on page 6105, right column, of Bast *et al.*, addresses why some marker tests do not obtain federal regulatory approval. It is not a requirement of the patent laws that a patent application be sufficiently established to obtain FDA approval, as "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled." See MPEP § 2164.05.

The Examiner also states that LaBaer, *J. Proteome Res.* 4: 1053-9, 2005, "teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting." Office Action, page 14. This, however, is nothing more than a recitation of basic considerations that the author believes should go into any biomarker discovery program. At most, the LaBaer publication provides a recitation of difficulties that *might* be encountered in practice. More appropriately, the LaBaer publication reflects considerations that are routine to one skilled in the field of biomarkers.

The Examiner further attempts to support the rejection (see page 14 of the Office Action) by reference to the following section from Baker, *Nature Biotechnology* 23: 297-304 (2005), page 298:

Walking on Thin Ice

> 'Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is;' says Ole Vesterqvist, director of clinical discovery at

> NewYork-based Bristol-Myers Squibb. 'You start walking, and you get comfortable. Then you break through.' Vesterqvist describes an example in which published clinical data showed that people with heart failure had higher levels of the peptide endothelin I (ET-1) compared to healthy controls, based on immunoassays. But in studies at Bristol-Myers Squibb, these patients showed no increase in plasma concentration of the peptide, Eventually, Vesterqvist's group found research revealing that the previous studies used an antibody that cross-reacted with the precursor to ET-1, big-ET. Although levels of the precursor are higher in patients with heart failure, the levels of ET-1 are not. Ironically, the Bristol-Myers Squibb assay did not produce the expected results because it was more specific for ET-1 than assays previously used in other laboratories.

The discussion to which the Examiner refers is nothing more than an anecdotal report of a rather simple error on the part of one researcher in one example. To the extent the passage is meaningful at all, it speaks to the need for a rather basic understanding of the biomarker with which one is working.

Applicants respectfully submit that the state of the prior art is one of common usage of biomarkers generally, and that each of the publications cited by the Examiner are consistent with this understanding. Furthermore, the specific classes of subject-derived markers recited in the claims are each well known to those of skill in the art.

C. The relative level of skill in the art

The skill in the art is extremely high. The skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis and prognosis of patients, and also has extensive experience in the generation and characterization of antibodies for use in such tests. As noted above with regard to the state of the art, the articles cited by the Examiner in the rejection emphasize that the skilled artisan is well aware of the potential pitfalls that might be encountered in practice. The artisan is prepared to perform the necessary studies to practice the claimed methods, and understands that the required methods are routine in the art.

D. The quantity of experimentation necessary

As noted above, claim 1 refers to a method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders. According to the claim, at least one subject-derived marker related to blood pressure regulation is used together with at least one subject-derived marker related to myocardial injury.

Additional markers from other art-recognized marker classes, for example, subject-derived markers related to coagulation and hemostasis, are referred to in various dependent claims.

As is also noted above, the specific classes of subject-derived markers recited in the various claims are well established in the art. In addition, the specification teaches specific examples of markers in each of the art-recognized classes of markers recited in the claims. The specification further provides examples as to how subject-derived markers related to blood pressure regulation (*e.g.*, ANP, BNP) and subject-derived markers related to myocardial injury (*e.g.*, cardiac troponin, myoglobin, CK-MB) may be used to distinguish between different cardiovascular disorders (such as congestive heart failure and cardiac ischemia and necrosis), and how the addition of markers related to coagulation and hemostasis (*e.g.*, D-dimer) can be used to further distinguish cardiovascular disorders (such as pulmonary embolism).

The Examiner appears to acknowledge that the specification is enabling for those embodiments specifically exemplified with data (Office Action, page 9). Applicants note that such methods can be practiced on any subject, and can be used to rule in or out (diagnose, and therefore distinguish between) a plurality of conditions, as required by the claims. Thus, at least with regard to troponin isoforms, B-type natriuretic peptide, and D-dimer, it appears undisputed that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The Examiner fails to acknowledge, however, that the skilled artisan can readily extrapolate the exemplary data in the specification regarding specific biomarkers to the general classes of molecules recited in the claims, as each is a representative of an art-recognized class having relationships to well known physiological pathways. Thus, data on molecules such as ANP and BNP can be extrapolated to markers related to blood pressure regulation, data on molecules such as cardiac troponin can be extrapolated to markers related to myocardial injury, data on molecules such as D-dimer can be extrapolated to markers related to coagulation and hemostasis, *etc.*

In view of the teachings of the specification and the knowledge available in the art, the quantity of experimentation required to practice the invention is no more than routine. The specification provides the artisan with detailed examples of which markers to use and which cardiovascular disorders are to be distinguished. It further informs the artisan of suitable

methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis. When properly considered, it is apparent that what the Examiner likens to "tossing out the mere germ of an idea" or "a general roadmap" (Office Action, page 12) is actually a complete description of how to make and use the claimed invention from start to finish.

Much of the Examiner's remarks in the rejection appear to be directed to the quantity of experimentation necessary. These remarks are based on the Examiner's personal opinion or are based on publications which, as discussed above, do not support the Examiner's position. In contrast to the extensive technical discussion in the specification, which the law presumes is enabling, the Examiner's personal opinion is not a sufficient rebuttal.

For example, based on the comments on page 10 and at the top of page 12 of the Office Action, the Examiner appears to believe that the claims must enable distinguishing amongst any and all possible cardiovascular disorders using any and all subject-derived markers and any and all sample types in order to satisfy the enablement requirement. Applicants submit that this is not required, either by the claims or by the enablement requirement. Instead, the claims simply relate to distinguishing amongst a plurality of (meaning at least two) cardiovascular disorders. And while it may be theoretically possible that certain unspecified cardiovascular conditions cannot be distinguished by the claimed methods using "all subject-derived markers in all sample types," as the Examiner alleges, the Board of Patent Appeals and Interferences has repeatedly pointed out in the context of enablement rejections that it is not the task of the claims to exclude such potentially inoperable embodiments:

> Nor are we concerned that the claims may include inoperable embodiments, as is it not a function of the claims to specifically exclude possible inoperative embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974).

Ex Parte Hicks, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.).

Moreover, the Examiner fails to give any weight to the fact that the skilled artisan can readily extrapolate the exemplary data in the specification regarding specific biomarkers to the general classes of molecules recited in the claims, as each is a representative of an art-recognized class having relationships to well known physiological pathways. Rather than analyze the claims

with knowledge generally available in the art, the Examiner focuses strictly on the number of possible markers in each class. *See*, Office Action, page 11. While it may be true that the specification discloses 18 potential "myocardial injury markers" for example, the Examiner does not provide any scientific evidence or reasoned scientific explanation as to why those markers could not each be used in the claimed invention as taught in the specification, and particularly in view of the data regarding cardiac troponin. As stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

The Examiner also appears to believe that only "specific markers" (that is, markers that are only affected by a specific disease state) can be used in the claimed methods, or indeed for diagnosis generally; that the skilled artisan would have to perform studies to "weed out" the nonspecific markers present in the various marker classes described in the specification and claims; and that such studies represent undue experimentation. This view is demonstrably incorrect.

For example, the Examiner refers to D-dimer and its use, relative to other markers of coagulation and hemostasis, in distinguishing pulmonary embolism as follows: "markers recited in claim 11 with an exception of D-dimer are not specific markers of pulmonary embolism... and so do not satisfy features of diagnostic markers for pulmonary embolism." *See*, Office Action, pages 15 and 16). In so stating, the Examiner is apparently unaware that D-dimer itself is not a "specific marker of pulmonary embolism." *See, e.g.*, Indik and Alpert, *Prog. Cardiovasc. Dis.* 42: 261-272, 2000 (cited by the Examiner in the Office Action), page 262 ("Since D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis in the body, the specificity of all DD assays is expected to be low"). Nevertheless, it is an FDA-approved test for use in the evaluation of pulmonary embolism, and so presumably does "satisfy features of diagnostic markers for pulmonary embolism," the Examiner's opinion with regard to nonspecific tests notwithstanding.

It must be acknowledged that, as demonstrated by the acceptance of the D-dimer test in the art, even nonspecific markers can be useful clinically when in the hands of the skilled artisan,

as the skilled artisan does not use diagnostic tests in an informational vacuum. Rather, diagnostic tests are used by skilled medical personnel in concert with other available medical indicia related to a subject. As discussed in paragraph [0075] of the present specification, "diagnosis" refers to a relative probability that a certain disease is present in the subject, and not the ability of a "specific marker" to give a definitive yes/no answer to the existence of a disease. Tests can be used to "rule in" a diagnosis, or to "rule out" a diagnosis by signaling an increased or decrease probability of a particular diagnosis. The fact that D-dimer is not specific for pulmonary embolism does not mean that it cannot fulfill its diagnostic role for the skilled artisan.[1]

Again, the Examiner does not provide any scientific evidence or scientifically-based explanation as to why the various markers of coagulation and hemostasis such as are described in the specification and claims could not each be used in the claimed invention as taught in the specification, and particularly in view of the data regarding D-dimer. Indeed, the art teaches that other markers of coagulation and hemostasis may be used in a similar fashion to D-dimer in the evaluation of pulmonary embolism. *See, e.g.*, LeCapra *et al., Blood Coagul. Fibrinolysis* 11: 371-7, 2000; Watanabe et al., Am. J. Hematol. 65: 35-40, 2000. (Copy of reference provided in association with an IDS filed herewith)

E. The predictability of the art

In the present case, the methods to be followed are all routine; the only factor required to practice the claimed invention is the understanding that such methods should be pursued, an issue that is solved by reference to the present specification and claims.

The Examiner's comments in the Office Action regarding the state of the prior art (discussed above) are also relevant to an understanding of the predictability of the art. As discussed in detail above, assertions such as there can be a "lengthy process of assay development," that "many markers that correlate with disease statistically may not prove to be useful clinically," or that "the process of converting such a biomarker into a practical clinical

[1] In fact, nonspecific tests are used constantly in medicine. Consider the well known "prostate-specific antigen" ("PSA") test. Elevated PSA levels may be caused by conditions including prostate cancer, benign prostate enlargement, inflammation, and infection, and elevations are understood to be affected by both age and race. Despite the fact that only 25 to 30 percent of men who have a biopsy due to elevated PSA levels actually have prostate cancer, the PSA test is routinely used by artisans for initial diagnosis and screening.

test" amount to broad allegations that the disclosure is speculative, coupled with a recitation of difficulties that *might* be encountered in practice. Such reasoning, however, is legally insufficient for rejecting a claim under the enablement requirement.

Applicants respectfully submit that the test of enablement is not whether certain scenarios may be constructed in which the invention might not work, but rather whether one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. The present specification and claims meet this standard.

F. The amount of direction or guidance

As the Examiner appears to acknowledge that the specification provides the artisan with several detailed examples of which markers to use for certain exemplary cardiovascular disorders to be distinguished. It further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis. When properly considered, it is apparent that what the Examiner likens the present invention to "tossing out the mere germ of an idea" or "a general roadmap" (Office Action, page 12) is actually a complete description of how to make and use the claimed invention from start to finish.

G. The presence or absence of working examples

The Examiner acknowledges that the specification provides exemplary data for various marker combinations "for distinguishing a plurality of cardiovascular disorders, but attempts to minimize the value of these examples by stating the examples "only include MI, congestive [ ] heart failure, acute coronary syndrome, unstable angina, and pulmonary embolism." Office Action, sentence bridging pages 11 and 12. The Examiner also acknowledges that the specification is enabling for a method for distinguishing between myocardial infarction and pulmonary embolism using subject-derived markers comprising troponin isoforms, B-type natriuretic peptide, and D-dimer. Office Action, page 9.

As discussed above, the Examiner seeks to limit the claims by focusing the question of enablement on what is present in the examples, while ignoring the remaining teachings of the specification. In the context of enablement rejections, the Federal Circuit has cautioned against

limiting a claimed invention to preferred embodiments or specific examples set forth in the specification. See, *Ex Parte Hicks*, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.) (citing *Texas Instruments v. U.S. Int'l Trade Comm.*, 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986)).

H. The breadth of the claims

The claims are circumscribed in their breadth, in that they refer to methods for distinguishing amongst a plurality of cardiovascular conditions that rely on measuring subject-derived markers from specified art-recognized classes of biomarkers.

The Examiner's comments concerning the breadth of the claims are largely irrelevant or fail to consider the knowledge available in the art. As noted above, the Examiner appears to believe that the enablement requirement requires the ability to distinguish all possible cardiovascular disorders. Office Action, pages 10 and 11. The claims, however, only require that the method distinguish between a plurality of cardiovascular disorders. The Examiner also appears to believe that enablement requires the ability to utilize all possible subject-derived markers in all sample types. Office Action, page 12, first full sentence. The claims instead only recite members of specific art-recognized classes of subject-derived markers.

Furthermore, the Examiner's focus on the number of subject-derived markers recited in the claims (Office Action, page 11) fails consider that the skilled artisan can readily extrapolate the exemplary data in the specification regarding specific biomarkers to the general classes of molecules recited in the claims, as each is a representative of an art-recognized class having relationships to well known physiological pathways.

I. Conclusion

In the present case, the skilled artisan can, by simply following the extensive detailed guidance in the specification, perform the claimed methods using nothing more that routine experimentation. In contrast, the rejection fails to consider the knowledge available in the art, being based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that *might* be encountered in practice. As such, the rejection does not present a sufficient basis for rejecting a claim under the enablement

requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3.

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

5. Rejection of claims 1-17 under 35 U.S.C. § 112, second paragraph

Applicants respectfully traverse the rejection of claims 1-17 under 35 U.S.C. § 112, second paragraph, as allegedly failing to comply with the definiteness requirement.

A. The Examiner asserts that the following use of the term "said markers" in claim 1 is allegedly indefinite:

> A method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders, comprising:
>
> assaying said sample for the presence or amount of one or more subject-derived markers related to blood pressure regulation, and for the presence or amount of one or more subject-derived markers related to myocardial injury, and
>
> characterizing said subject's risk of having developed or of developing each of said plurality of cardiovascular disorders based upon the presence or amount of **said markers**, wherein the amount of one or more of said markers is not compared to a predetermined threshold amount.

To the contrary, the claim states that a sample is analyzed "for the presence or amount of one or more subject-derived markers related to blood pressure regulation, and for the presence or amount of one or more subject-derived markers related to myocardial injury." The next section of the claim, which refers to "said markers" clearly refers to the one or more subject-derived markers recited in the previous step.

The threshold for establishing indefiniteness is very high. A claim must reach the level of being "insolubly ambiguous" in order to be indefinite. See, e.g., *Scripps Research Institute v.*

Nemerson and Konigsberg, 78 U.S.P.Q.2d 1019, 1030 (Bd. Pat. App & Interf. 2005). Applicants respectfully submit that the Examiner has not applied this rigorous standard to the present claims.

Nevertheless, in an effort to advance prosecution, Applicants have amended claim 1 to refer to an analysis step (a) in which certain markers are detected, and to unambiguously state that the markers referred to in characterization step (b) are those markers measured in the analysis step. Applicants respectfully submit that the amendment renders the rejection moot, and request that it be reconsidered and withdrawn.

B. The Examiner asserts that the following use of the term "said markers" in claim 2 is allegedly indefinite:

> A method according to claim 1, wherein said characterization step is performed without comparing the amount of **any of said markers** to a predetermined threshold amount.

As in the case of claim 1, Applicants have amended claim 2 to again state that the markers referred to in characterization step (b) are those markers measured in the analysis step. Applicants respectfully submit that the amendment renders the rejection moot, and request that it be reconsidered and withdrawn.

C. With regard to the Examiner's comments concerning claim 4, Applicants respectfully submit that the claim as originally written is not insolubly ambiguous. In this regard, Applicants note the quote from *Scripps Research Institute v. Nemerson and Konigsberg,* cited above, which states that "even if construction is difficult and the result equivocal, the claim is nevertheless definite," and the fact that the Examiner's comments at best indicate an equivocal construction.

Nevertheless, Applicants have amended claim 4 herein to assist the Examiner's understanding of the claim. Applicants respectfully submit that the amendment renders the rejection moot, and request that it be reconsidered and withdrawn.

D. With regard to the Examiner's comments concerning claim 8, Applicants respectfully submit that the claim as originally written is not insolubly ambiguous, as the Examiner's comments at best indicate an equivocal construction.

Nevertheless, Applicants have amended claim 8 herein to assist the Examiner's understanding of the claim. Applicants respectfully submit that the amendment renders the rejection moot, and request that it be reconsidered and withdrawn.

E. With regard to the Examiner's comments concerning claim 12, Applicants respectfully submit that the claim as originally written is not insolubly ambiguous, as the Examiner's comments at best indicate an equivocal construction.

Nevertheless, Applicants have amended claim 12 herein to assist the Examiner's understanding of the claim. Applicants respectfully submit that the amendment renders the rejection moot, and request that it be reconsidered and withdrawn.

F. With regard to the Examiner's comments concerning claim 14, Applicants respectfully submit that the claim as originally written is not insolubly ambiguous, as the Examiner's comments at best indicate an equivocal construction.

Nevertheless, Applicants have amended claim 14 herein to assist the Examiner's understanding of the claim. Applicants respectfully submit that the amendment renders the rejection moot, and request that it be reconsidered and withdrawn.

G. With regard to the Examiner's comments concerning claim 17, Applicants respectfully submit that amendment to the claim renders the rejection moot.

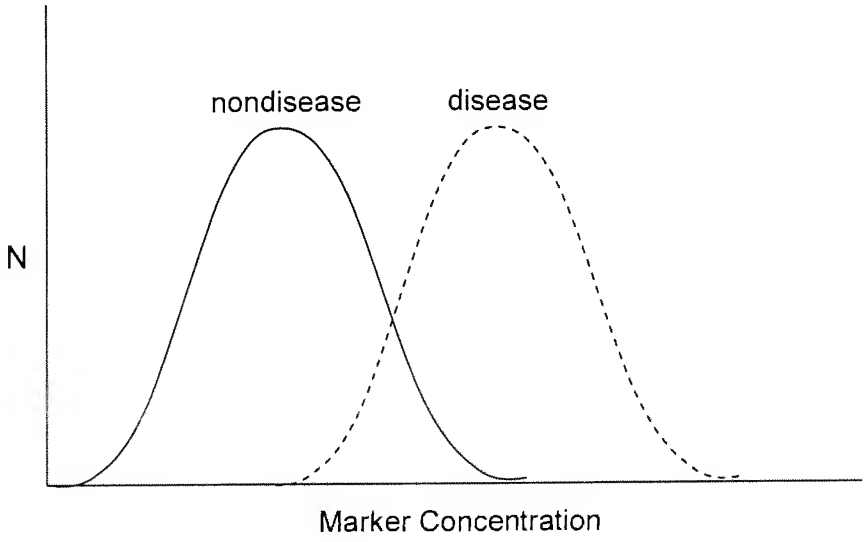
6. Rejection of claims 1-4, 9-12, 15 and 16 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-4, 9-12, 15 and 16 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski, U.S. Patent 5,710,008, in view of Buechler *et al.*, U.S. Patent 5,795,725, Baig, *Am. Heart J.* 135: S216-230, 1998, Kline *et al.*, *Ann. Emerg. Med.* 35: 168-80, 2000, and Zweig *et al.*, *Clin. Chem.* 39: 567-77, 1993.

Claim 1 and its dependent claims all contain the following limitation: that the subject's risk of having developed or of developing each of said plurality of cardiovascular disorders is characterized based upon the presence or amount of the markers measured, wherein the amount of one or more of said markers is not compared to a predetermined threshold amount.

With respect to the underlined limitation, the Examiner relies entirely on the Zweig *et al.* publication, acknowledging that none of the other cited publications disclose or suggest the use of markers without comparison to some predetermined threshold. Zweig *et al.*, however, is not directed to the use of markers for characterizing individual subject's disease risk without comparing markers to a predetermined threshold, as the Examiner asserts. Instead, Zweig *et al.* describes the use of Receiver-Operator Characteristic ("ROC") plots to evaluate the performance of a laboratory test (the ability of the test to discriminate a diseased population from a nondiseased population).

Applicants provide herewith a declaration by Dr. Joseph Anderberg, explaining generally the use of ROC analysis in diagnostic test design, and discussing the teachings of the Zweig *et al.* publication. As Dr. Anderberg indicates in paragraph 4 of his declaration, when examining a marker of interest for its ability to distinguish disease from nondisease, one typically measures the marker in these two populations. Typically, the populations will exhibit some overlap in marker values:



Any particular marker concentration chosen as a diagnostic threshold will include some number of either false negatives (if the threshold is within the diseased population, but outside the overlap region), false positives (if the threshold is within the nondiseased population, but outside the overlap region), or both false negatives and false positives (if the threshold is within the overlap region). Anderberg Declaration, paragraph 5.

As described in some detail in Zweig *et al.*, ROC analysis can be used to determine the clinical performance of this (or any) test, which, as noted in the first paragraph of Zweig *et al.*, refers to "the ability to correctly classify subjects into clinically relevant subgroups." As shown in Fig. 4 of Zweig *et al.*, in ROC analysis, one plots the sensitivity (the "true positives") against 1-specificity (the "true negatives") in the two populations. Anderberg Declaration, paragraph 6. Examples of such "ROC plots" are shown in Figs. 4-12 of Zweig *et al.*.

Dr. Anderberg explains that, as discussed in the first incomplete paragraph on page 565 of Zweig *et al.*, each point on the ROC plot represents a sensitivity/specificity pair corresponding to a particular threshold concentration. A theoretical "perfect test" curve would pass through the upper left corner of the ROC plot; a theoretical test that cannot discriminate between the two groups would produce a 45° line extending from the lower left corner of the ROC plot. The difference between these two extremes exhibited by the actual test can be used to provide a quantitative value concerning the ability of the test to distinguish disease from nondisease (for example as an area under the ROC curve, as discussed on page 568, right column, of Zweig *et al.*). Anderberg Declaration, paragraph 6.

Dr. Anderberg also points out that evaluating the ability of a particular test to discriminate a diseased <u>population</u> from a nondiseased <u>population</u> is completely different from using a test to evaluate the disease state of an <u>individual</u>, which is the subject matter of the present claims. As described in Zweig *et al.*, ROC analysis is used for the former, but not the latter. Thus, ROC analysis can be used to help *guide the selection of a diagnostic threshold*, as discussed beginning on page 571, right column, of Zweig *et al.* But Zweig *et al.* advises that "to use the test for **<u>patient management</u>**, a decision threshold **<u>must</u>** be selected." Page 572, first incomplete paragraph, emphasis added. Dr. Anderberg explains that Zweig *et al.* does not contemplate the claimed limitation of using a marker value in patient management without

comparing to a predetermined threshold , and, in fact, teaches that one cannot do so. Anderberg Declaration, paragraph 8.

Thus, contrary to the Examiner's belief, Zweig *et al.* not only fails to describe the use of markers for characterizing individual subject's disease risk without comparing markers to a predetermined threshold, but it teaches that one cannot do so.

Because the combination of publications cited by the Examiner do not teach or suggest each and every limitation of the claims, and because the cited publications actually teach away from the claimed methods, Applicants respectfully submit that no prima facie case of obviousness has been established. In view of the foregoing, request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

7. Rejection of claims 5-8, 13 and 14 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 5-8, 13 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski in view of Buechler *et al.*, Baig, Kline *et al.*, and Zweig *et al.*, and in further view of Holvoet *et al.*, U.S. Patent 6,309,888.

As discussed in detail above, the rejection relies on Zweig *et al.* publication as allegedly disclosing the use of diagnostic markers for characterizing individual subject's disease status without comparing markers to a predetermined threshold. In fact, Zweig *et al.* teaches that one cannot do so.

Because the combination of publications cited by the Examiner do not teach or suggest each and every limitation of the claims, and because the cited publications actually teach away from the claimed methods, Applicants respectfully submit that no prima facie case of obviousness has been established. In view of the foregoing, request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

8. Rejection of claim 174 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 5-8, 13 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Jackowski in view of Buechler *et al.*, Baig, Kline *et al.*, and Zweig *et al.*, and in further view of Heeschan *et al.*, *The Lancet* 354: 1757-62, 1999.

As discussed in detail above, the rejection relies on Zweig *et al.* publication as allegedly disclosing the use of markers for characterizing individual subject's disease status without comparing markers to a predetermined threshold. In fact, Zweig *et al.* teaches that one cannot do so.

Because the combination of publications cited by the Examiner do not teach or suggest each and every limitation of the claims, and because the cited publications actually teach away from the claimed methods, Applicants respectfully submit that no prima facie case of obviousness has been established. In view of the foregoing, request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

9. Obviousness-Type Double Patenting

The Examiner has issued 21 pages of provisional obviousness-type double patenting rejections. In each case, the rejections are improperly founded on the "teachings" of various copending patent applications in combination with various secondary publications. *See, e.g.*, Office Action, page 30, last incomplete paragraph; page 32, first paragraph; page 33, second paragraph; *etc.*

As described in MPEP § 804, any obvious-type double patenting rejection should make clear: (A) the differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and (B) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent or copending patent application. As is also noted in MPEP § 804, the disclosure of the patent may not be used as prior art in analyzing claims for obviousness-type double patenting.

Nowhere in the rejections does the Examiner analyze the conflicting claims. Furthermore, by focusing on the "teachings" of each copending application rather than the claims, the Examiner appears to have used the various copending patent disclosures as prior art.

By failing to perform the type of analysis required in any obvious-type double patenting rejection, Applicants have been deprived of a meaningful opportunity to respond to the various rejections. Should the rejections be maintained, Applicant respectfully requests that the correct

analysis be presented in a non-final office action, so that Applicants may be afforded an opportunity to reply to the Examiner's comments.

Additionally, no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. See MPEP 804 (I)(B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.") In the event that other rejections of the present claims are successfully overcome by the current communication, withdrawal of the instant provisional rejections would be appropriate. Applicants authorize the examiner to follow MPEP 804 (I)(B) and allow the case without issuing a further Office Action should the provisional obviousness type-double patenting rejection be the sole remaining issue in the case.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 01/11/2007

By _____

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